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EXAMINER	
HOWARD, ZACHARY C	

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1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/977,864	DUDEK ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13,19-21 and 23-25* is/are pending in the application.

4a) Of the above claim(s) *4,6-13,19,20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,21 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,3-13,19-21 and 23-25* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 6/18/07 has been entered.

Claims 1 and 21 are amended. Claims 14-18 are currently canceled (Claims 2 and 22 were previously canceled). No new claims are added.

Claims 4, 6-13, 19 and 20 remain withdrawn as from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention or a non-elected species. This application contains claims 10-13, 19 and 20 drawn to an invention nonelected with traverse in Applicant's response filed 9/14/05.

Claims 1, 3, 5, 21 and 23-25 are under consideration in the instant application, as they read upon the elected species of colon cancer and hedgehog antibody.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (10/18/06).

All objections to and/or rejections of claim 17 are moot in view of Applicants' cancellation of this claim.

The objections to claims 1 and 21 at pg 8 are withdrawn in view of Applicants' amendments to these claims.

Maintained Objections and/or Rejections

Claim Rejections – 35 USC § 112, 1st paragraph, written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 21 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set previously and maintained at pg 4-8 of the 10/18/06 Office Action.

In view of Applicants' amendments to the claims, the basis of the rejection is first restated and then Applicants' arguments are addressed.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

The claims are genus claims because the claims encompass methods of inhibition of unwanted cell proliferation using a plurality of antibodies encompassed by the term "*hedgehog* antibody". The term "*hedgehog* antibody" encompasses antibodies that bind to a large genus of proteins with different amino acid sequences. First, the specification teaches "the term "hedgehog" is used to refer generically to any member of the hedgehog family, including the sonic, indian, desert and tiggy-winkle. The term may be used to indicate protein or gene" (pg 17). Second, the specification further describes a variety of hedgehog mutant proteins (pg 81-88). The specification teaches that these mutant proteins include those with one or more mutations (additions, deletions and substitutions) to the sequence of the protein. Third, the term "*hedgehog* antibody" also broadly encompasses antibodies to any member of the *hedgehog* signaling pathway (including *gli-1*, *gli-2*, *gli-3*, *patched*, *smoothened*, and other undisclosed components of the pathway). In summary, the term "*hedgehog* antibody" encompasses a large genus of antibodies to Sonic, Indian, Desert, or Tiggy-winkle hedgehog proteins or nucleic acids, antibodies to variants of said proteins and nucleic acids, and antibodies to members of Sonic hedgehog signaling pathway (*gli-1*, *gli-2*, *gli-3*, *patched*, *smoothened* and other undisclosed components of the pathway). However, the instant specification

fails to describe the entire genus of *hedgehog* antibodies that will work with the claimed methods of treatment.

From the specification, it is clear that Applicants have possession of a method of inhibiting proliferation of several cancerous tissues (e.g., prostate or colon) that overexpress *gli-1* or *Sonic hedgehog* by using a specific *Sonic hedgehog* antibody (5E1). The 5E1 antibody is described in the prior art as a monoclonal antibody to the biologically active 19kDa N-terminal proteolytic fragment of the Sonic hedgehog (Shh) protein. Therefore, Applicants describe a single monoclonal antibody to the N-terminal fragment of Shh protein that works in the claimed method. Applicants do not describe the epitope on the N-terminal fragment of Shh protein to which the 5E1 antibody reacts. Applicants do not describe any other antibody to a Shh protein, or a mutated variant of a Shh protein, that will function to inhibit unwanted cell proliferation. Applicants do not describe any fragment or other mutant of the Shh protein that will generate antibodies that will inhibit the activity of the biologically active 19kDa N-terminal Shh fragment. Furthermore, Applicants do not describe any antibodies to Indian, Desert, or Tiggy-winkle hedgehog proteins that function to inhibit unwanted cell proliferation, nor is there a description of the activity of Indian, Desert or Tiggy-winkle hedgehog proteins playing a role in unwanted cell proliferation. Furthermore, Applicants do not describe any antibodies to other components of the Sonic hedgehog signaling pathway that function to inhibit unwanted cell proliferation, nor is there a description of the activity of any other component of the hedgehog signaling pathway playing a role in unwanted cell proliferation. Many of these components are intracellular, and there is no description of an antibody to an intracellular hedgehog pathway component that will inhibit unwanted cell proliferation when applied extracellularly to a tissue (in contrast, the biologically active 19kDa Sonic hedgehog protein is a secreted protein that acts extracellularly). Finally, Applicants do not describe any particular antibodies to any nucleic acids that inhibit unwanted cell proliferation. Again, these nucleic acids are found intracellularly and there is no description of an antibody to an intracellular nucleic acid that will inhibit unwanted cell proliferation when applied extracellularly to a tissue. In summary, the specification fails to describe the entire genus of proteins or nucleic acids, that when

bound by an antibody, will result in inhibition unwanted cell proliferation, and therefore the specification fails to describe the entire genus of antibodies that will work in the claimed methods.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of *hedgehog* antibodies to be used in the claimed methods. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish antibodies in the genus are missing from the disclosure. There is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the antibodies encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed antibodies as being functional in inhibiting unwanted cell proliferation as the 5E1 monoclonal hedgehog antibody. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the genus of *hedgehog* antibodies that would work to inhibit unwanted cell proliferation, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a method of using a hedgehog monoclonal antibody 5E1 to inhibit unwanted cell proliferation of cells overexpressing the *gli-1* gene, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Applicants' arguments (6/8/07; pg 13-15) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the claimed invention is not primarily based on identifying specific hedgehog antibodies but rather lies in the combination of the diagnostic step of determining whether a diseased or disordered tissue overexpresses a *gli-1* gene or *hedgehog* gene and the recognition that hedgehog antibodies can be used to treat said tissues. Applicants argue that the question is not whether Applicants were in possession of the invention because the specification provides literal support for the claims. Applicants argue that there is a strong

presumption that adequate written description is present in an application as filed. Applicants point to *In re Wertheim* (1976).

Applicants' arguments have been fully considered but are not found persuasive. Applicants' characterization of *In re Wertheim* (1976) is not disputed. However, the rejection set forth previously and maintained herein satisfies the burden of presenting reasons why the skilled artisan would not recognize in the disclosure a description of the invention defined by the claims. The instant claims are directed to methods of inhibiting unwanted cell proliferation that require use of a genus of "*hedgehog* antibodies" that bind to a large genus of variant proteins. As such, adequate written description of the claimed methods requires written description of the genus of "*hedgehog* antibodies" that are functional in inhibiting unwanted cell proliferation. As described above, this genus encompasses antibodies to a vast number of proteins, including other hedgehog proteins (e.g., Indian, Desert, Tiggy-winkle) and nucleic acids, variants of hedgehog proteins with one or more mutations, and antibodies to members of the hedgehog signaling pathway (*gli-1*, *gli-2*, *gli-3*, *patched*, *smoothened* and other undisclosed components of the pathway). The specification fails to provide a sufficient description of encompassed antibodies that will function to inhibit unwanted cell proliferation in order to demonstrate that Applicants were in possession of the genus at the time of filing. Instead, the specification describes only a single species of "*hedgehog* antibody" that will work in the claimed methods: the monoclonal hedgehog antibody 5E1 (which binds to the Sonic hedgehog protein and inhibits its activity).

Applicants further argue that other hedgehog antagonists were known in the art. Applicants point to Baxter, U.S. Patent No 6,545,005.

Applicants' arguments have been fully considered but are not found persuasive. The instant application does not incorporate or otherwise refer to Baxter et al, U.S. Patent No 6,545,005 (published 4/8/2003) or the U.S. application from which it originated (09/663,835, filed 9/15/00). The instant application was filed 10/15/2001. Therefore, at the time of filing, the '005 patent had not been published. Furthermore, Baxter does not provide any support for a genus of "*hedgehog* antibodies" that inhibit unwanted cell proliferation. In contrast to molecules encompassed by the term

"*hedgehog* antibodies" (described above), Baxter provides only limited teachings regarding small molecule antagonists of the *Sonic hedgehog* signaling pathway. Such small molecules do not provide a description of antibodies that will functionally inhibit unwanted cell proliferation.

Applicants argue (pg 6) that written description for the claimed methods does not require that all possible "hedgehog antagonists" are known in the art. Applicants compare the term to the term "solvent". Applicants argue that the term "solvent" has written description despite the fact that new solvents may be discovered. Applicants further argue (pg 7) that the knowledge in the relevant art "supports that the "hedgehog antibody" term would be of recognized meaning".

Applicants' arguments have been fully considered but are not found persuasive. The term "solvent" in the relevant art is not analogous to the term "*hedgehog* antagonist" or "*hedgehog* antibody". The term "solvent" is a term that has been used in the chemical arts for decades with numerous species of solvents being thoroughly described by the prior art. In contrast, the term "*hedgehog* antibody" is a novel biological term used in the instant application to describe a genus of antibodies to all proteins or nucleic acids that meet the definition of "hedgehog". The claimed methods require use of those antibodies within said genus that are functionally capable of inhibiting unwanted cell proliferation. The specification does not describe a sufficient number of species to indicate that Applicants were in possession of the genus, and the knowledge in the art at the time of filing does not provide compensatory teachings.

In response to the argument that the disclosure fails to particularly identify any conserved structure or function of the intended antibodies, Applicants argue that the claims recite "hedgehog antibodies" and the specification provides "good guidance of the nature of the hedgehog genes and proteins to which the hedgehog antibodies apply". Applicants point to pages 1-7, 17-18 and 88 as providing guidance as to the nature of the antibodies with the necessary antagonist activity to be used in the claimed methods, and "how to construct and screen libraries for antibodies having suitable anti-proliferative activity". Applicants further argue (pg 7) that knowledge of "hedgehog genes and proteins" and "at least one known hedgehog antagonist antibody is such that

one of ordinary skill in the art would have a reasonable knowledge of the epitopes applicable to provide suitable antibodies, particularly using known screening methods.

Applicants' arguments have been fully considered but are not found persuasive. The specification at page 1-7, 17-18 and 88 describes how to make to antibodies to various proteins and/or nucleic acids, including hedgehog proteins and members of the *hedgehog* signaling pathway. At pg 8, the specification suggests that antagonist antibodies can be identified by administering candidate antibodies "to cells expressing a *hedgehog* reporter gene, and antibodies that cause decreased reporter gene expression are antagonists". The specification also describes a single antagonist antibody that binds to the *Sonic hedgehog* protein and also inhibits unwanted cell proliferation. The description on these pages, and in the rest of the specification, has been fully considered but is not sufficient to describe the genus of "*hedgehog* antibodies" that will function in inhibition of unwanted cell proliferation. The specification does not provide a description of the activity of antibodies to other members of the hedgehog protein family, antibodies to variants of hedgehog proteins, or antibodies to other known and unknown members of the hedgehog signaling pathway. Applicants have not provided a reasonable correlation between the activity of antibody to the *Sonic hedgehog* protein and the potential activity of these other antibodies. The specification merely suggests that some of these antibodies may be antagonists that will function and in claimed invention and suggests potential methods of screening for such antagonists (which may or may not actually result in identification of any inhibitory antibodies). As stated above, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645

(Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 5, 21 and 23-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 25 of copending Application No. 10/652,298. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

It is noted that the claims of '298 application were amended on 6/8/07.

Claims 1, 3, 5, 21 and 23-25 of the instant application are each anticipated by claim 25 of '864 because the instant claims are each preferred embodiments of claim 25 of '864, as taught by the specification of '864.

The method steps of claim 1 are identical to those of claim 25 of '864, except that instant claim is limited to determining *gli-1* overexpression whereas claim 25 of '864 encompasses any "*hedgehog* gene". However, the portion of the specification concerning claim 25 discloses *gli-1* as a preferred embodiment of the "*hedgehog* gene" to be measured; see also claim 1 of '864, which specifically recites determination of *gli-1* overexpression.

The method steps of claim 3 are identical to those of claim 25 of '864, except that the instant claim is limited to determining *gli-1* overexpression, and the tissue is limited to one expressing "cancer", whereas claim 25 of '864 encompasses any "*hedgehog* gene" and any diseased tissue. However, the portion of the specification concerning claim 25 discloses *gli-1* as a preferred embodiment of the "*hedgehog* gene" to be

measured; and "cancer" as a preferred embodiment of the diseased tissue to be measured; see also claim 28 of '864, which specifically recites that the tissue exhibits "cancer".

The method steps of claims 5, 21 and 23-25 are identical to those of claim 25 of '864, except that instant claims are limited to determining *gli-1* overexpression, and the tissue is limited to several species including "colon cancer", whereas claim 25 of '864 encompasses any "*hedgehog* gene" and any diseased tissue. However, the portion of the specification concerning claim 25 discloses *gli-1* as a preferred embodiment of the "*hedgehog* gene" to be measured; and "colon cancer" as a preferred embodiment of the diseased tissue to be measured; see also claim 5 of '864, which specifically recites that the tissue is associated with "colon cancer".

In the 6/18/07 response (pg 7), Applicants traverse the rejection and state that filing a terminal disclaimer "would be premature at this point because both applications are still pending and are subject to rejections".

The Examiner acknowledges Applicants' argument. However, the provisional rejection is maintained because at the time of this Office Action the pending claims of Application 10/652,298 render the instant claims (provisionally) unpatentable under the judicially created doctrine of obviousness-type double patenting.

New Objections and/or Rejections

Claim Objections

Claim 1 is objected to because of the following informalities:

Claim 1 is objected to because the recitations "said tissue overexpress" and "said tissue that overexpress" are grammatically incorrect. The word "overexpress" should be replaced with the word "overexpresses".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is indefinite because the elements recited in the claims do not constitute proper Markush groups. Specifically, the claim is indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. See MPEP § 2173.05(h).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Wallace et al, 12 April 1999. Current Biology. 9: 445-448.

As amended, claim 1 is drawn to a method of inhibiting unwanted cell proliferation in a tissue comprising determining whether said tissue overexpresses a *gli-1* gene and contacting said tissue with an effective amount of a *hedgehog* antibody, whereby the antibody causes decreased cell proliferation.

The specification provides two examples of "unwanted cell proliferation", including cancer and benign prostatic hyperplasia (pg 8), but does not provide a limiting definition of the phrase. Therefore, the phrase has been broadly interpreted to encompass any form of intentional inhibition of cell proliferation, because the intent to inhibit cell proliferation indicates that said proliferation is not wanted.

Wallace teaches that in postnatal murine cerebellum, "[c]ells expressing the genes *Ptc*, and *Gli1* were located in the EGL [external granule layer] and in the PC [Purkinje cell] layer (Figure 1a, b, d, e)" (pg 445). Wallace further teaches, "Ptc and Gli

genes were expressed in the outer layer of the EGL, where proliferating cells are located, suggesting that the genes are expressed mainly in dividing precursor cells" (pg 445). Wallace does not detect expression of *Gli1* in surrounding cells of the EGL. Therefore, the cells in the outer layer of the EGL with detectable *Gli1* expression meets the limitation of tissue that "overexpress a *gli-1* gene" (as recited in claim 1). Wallace further teaches, "To determine whether Shh plays a part in normal EGL development, I injected hybridoma cells that secrete neutralizing anti-Shh monoclonal antibodies (5E1 cells; [6]) into the brains of postnatal day 1 (P1) mice" (pg 445) with results including "[t]he EGL was also thinner, and the folia were not as deep in the anti-Shh-treated animals compared with controls (Figure 2)." This indicates that the hedgehog antibody caused decreased cell proliferation. As described above, the intent to inhibit cell proliferation indicates that the cell proliferation was unwanted. Therefore, Wallace anticipates instant claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahmane et al #1 (1997. Nature. 389: 876-881; cited as reference CA on the 10/27/03 IDS) in view of Dahmane et al #2 (1999. Development. 126: 3089-3100).

Dahmane et al #1 teach, "[s]ections of freshly excised human BCCs [basal cell carcinomas] were analysed by in situ hybridization. All but one of the samples examined showed unambiguous expression of Gli1, although the level of expression varied" (pg 877). The legend on pg 878 for Figure 2 shows "normal skin distal from tumorigenic regions in a BCC excision showing the absence of Gli1 expression". Therefore, Dahmane et al #1 teach that human BCCs overexpress the *gli-1* gene as compared to

normal skin. Dahmane et al #1 further teach, "[i]ndependent of whether Shh can initiate BCC formation, its expression in BCCs suggests a mode of autocrine tumour maintenance as secreted Shh from the tumour cells could activate its signaling pathway, leading to new expression of *Gli1*" (pg 880). Dahmane et al #1 further teach, "[t]he recurrence of BCCs [basal cell carcinomas] at sites adjacent to previous tumors could result from the observed ectopic expression of Gli1 in basal cells in a wide region extending beyond the neoplastic sites. This raises the possibility that Gli1 expression in basal cells is an early event and could be used as a diagnostic tool. Finally, therapeutic agents for BCCs are likely to include inhibitors of the Shh signaling pathway and Gli function" (pg 880). Dahmane does not teach a *hedgehog* antibody as therapeutic agent for treating BCC.

Dahmane et al #2 teach, "anti-Shh blocking antibodies" (pg 3094) from "hybridoma 5E1 secreting anti-Shh IgG antibody" (pg 3091).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to measure Gli1 expression in sporadic basal cell carcinoma to determine if it is overexpressed compared to normal skin (as taught by Dahmane et al #1) and to further contact a sporadic basal cell carcinoma that overexpresses Gli1 with a *hedgehog* antibody as taught by Dahmane et al #2. The person of ordinary skill in the art would have been motivated to make that modification because Dahmane suggests the use of Gli1 for diagnosis and the use of an inhibitor of the Shh signaling pathway as a therapeutic agent for BCC, but is silent as to the specific nature of any inhibitors of the Shh signaling pathway, and Dahmane et al #2 teaches a specific antibody inhibitor of the Shh signaling pathway. The person of ordinary skill in the art would have had a reasonable expectation of success in practicing said method because Dahmane et al #1 teaches secreted Shh as a mode of autocrine tumor maintenance, and the blocking antibody to Shh taught by Dahmane et al #2 would block the ability of secreted Shh to activate its receptor.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646